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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,280	03/01/2005	John S. Wai	21161YP	8333

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,280	WAI, JOHN S.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-18* is/are allowed.

6)☒ Claim(s) *19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050301 & 20070430*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an infection in a patient due to HIV-1 integrase, does not reasonably provide enablement for a method of inhibiting HIV integrase generally; or a method of **preventing** or treating infection by HIV in a subject generally; or for **preventing**, treating or delaying the onset of AIDS in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 19 recites 'a method of inhibiting HIV integrase in a subject' and the specification fails to enable one skilled in the art for the recited use. The instant claim appears to be in 'reach-through' format. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification. Further, there is no disclosure regarding how the patient in need of such activity is identified and further, how an inhibition of HIV integrase is generally produced in the patient. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art.

Claim 20 is drawn to 'a method for **preventing** or treating infection by HIV or for **preventing**, treating or delaying the onset of AIDS in a subject'. The specification fails to enable one skilled in the art for the recited use. The scope of the method claims is not adequately enabled solely based on the test assays to measure the inhibition activity provided in the specification at page 63. First, the instant claims cover 'a method of inhibiting the function of the HIV integrase' generally or 'a method for the treatment of conditions associated with HIV integrase' generally, which for example, includes conditions caused by HIV-1, HIV-2, etc. that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents having HIV integrase inhibition activity, useful to treat all types of HIV infections, which include AIDS, etc. Test procedures and assays relied upon at page 63 are drawn to inhibition of HIV-1 integrase (based on the references Wolfe et al., J. Virol. 1996, Hazuda et al., J. Virol. 1997 cited in the specification). The specification does not provide which compounds were

tested, however, it is generally concluded that the representative compounds of the invention demonstrated inhibition activity. There is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of **all** types of conditions associated with HIV integrases embraced by the instant claims. One of ordinary skill would not know to extrapolate this test data to compounds having the assorted types of substituents provided in the instant claims. The disorders encompassed by the instant claims include AIDS, etc., some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

State of the art references provide that:

(1) <http://www.hivguidelines.org/Content.aspx?PageID=526>

Little is known to date about the effectiveness of current antiretroviral medications against HIV-2 infection, in part, because antiretroviral medications have not been widely available in areas with large numbers of HIV-2 infection. Little is known about whether the current emphasis on early initiation of combination antiretroviral therapy for HIV-1 is appropriate for treatment of HIV-2. Viral load testing, which has become an important tool in treatment planning and monitoring for HIV-1 is not currently available for HIV-2.

(2) <http://www.acgis.com/aidsline/1992/nov/M92B0027.html>

Calanolides A (1) and B (4) were completely protective against HIV-1 replication and cytopathicity (EC_{50} values of 0.1 microM and 0.4 microM, respectively), but were inactive against HIV-2.

Further, the instant claims are directed to 'a method for preventing or treating infection by HIV or for **preventing**, treating or delaying the onset of AIDS in a subject' and 'a method of inhibiting the HIV integrase in a subject' which is not sufficiently established in the specification. The biological test assays are provided in the specification page 63, however, these assays are directed to determining the *in vitro* anti-HIV activity of the compounds in an HIV-1 integrase assay and there is insufficient evidence that such studies correlate with *in vivo* efficacy in treatment of all diseases associated with HIV integrases generally, particularly in humans. The obstacles to therapy of HIV are well documented in the literature, which include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus; and 2) the complexity and variation of the pathology of HIV infection in different individuals. HIV-specific immunity can control viral replication and delay disease progression but does not clear infection. Antiretroviral treatment consists of inhibitors that target for viral entry, reverse transcriptase, and viral protease. Therapy can control viral replication, restore immunity, and delay disease progression, but it cannot eliminate infection.

Marcus et al. (see the enclosed PubMed Abstract), in their recent publication expressed that 'despite advances, the global spread of HIV and especially its spread in developing countries continues almost unabated'. Also, van Heeswijk et al., (PubMed Abstract enclosed) stated that, "further clinical studies are needed to identify optimal combinations for treatment of antiretroviral naive and experienced HIV-1 infected patients". Despite the unprecedented

successes in the therapy of HIV infection, AIDS remains a major world health problem being the first cause of death in Africa and the fourth leading cause of death worldwide. Despite the success of protease and reverse transcriptase inhibitors, new drugs to suppress HIV-1 replication are still needed. Thus it is clear from the above evidence that the ability to treat diseases associated with HIV is highly unpredictable and has met with very little success.

Furthermore, the scope of the claim is not adequately enabled solely based on the assay procedures to measure the integrase inhibitory activity provided in the specification. The instant claim is drawn in part to a method of '**prevention** of HIV infection or **prevention** of AIDS', which is not remotely enabled. The instant compounds are disclosed to have anti-HIV activity and it is recited that the instant compounds are useful in the '**prevention**' of infection by HIV, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "preventive" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease or disorder claimed herein.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Use of the compounds in treatment as well as prevention of HIV infection.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat and/or prevent HIV infection generally. The CDC website provides that "At present, no therapy exists to eliminate the human immunodeficiency virus (HIV) or restore an immune system damaged by it. Currently, no vaccine exists to protect susceptible persons from infection." (see http://wonder.cdc.gov/wonder/prevguid/p0000072/p0000072.asp). Further, Miles (2005 Medline abstract enclosed) indicate that "Well into the third decade of the HIV pandemic, there is still no cure on the horizon and recent results of preventive vaccine studies have been disappointing".

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders cited, etc. nor there are doses given for the treatment of the disorders recited. The specification provides test procedures (see page 63) and it is concluded that the compounds of the invention demonstrated inhibitory activity. However, there is no disclosure regarding how the *in vitro*

results correlate to treatment as well as **prevention** of all types of diseases due to infection by HIV.

6) The breadth of the claims: The instant claims embrace treating or **preventing** all diseases associated with HIV infection.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Allowable Subject Matter

Claims 1-18 are allowed. The references of record do not teach or fairly suggest the instantly claimed compounds, see e.g., U.S. Patent No. 5,821,241.

Receipt is acknowledged of the Information Disclosure Statements filed on March 1, 2005 and April 30, 2007 and copies are enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

November 28, 2007